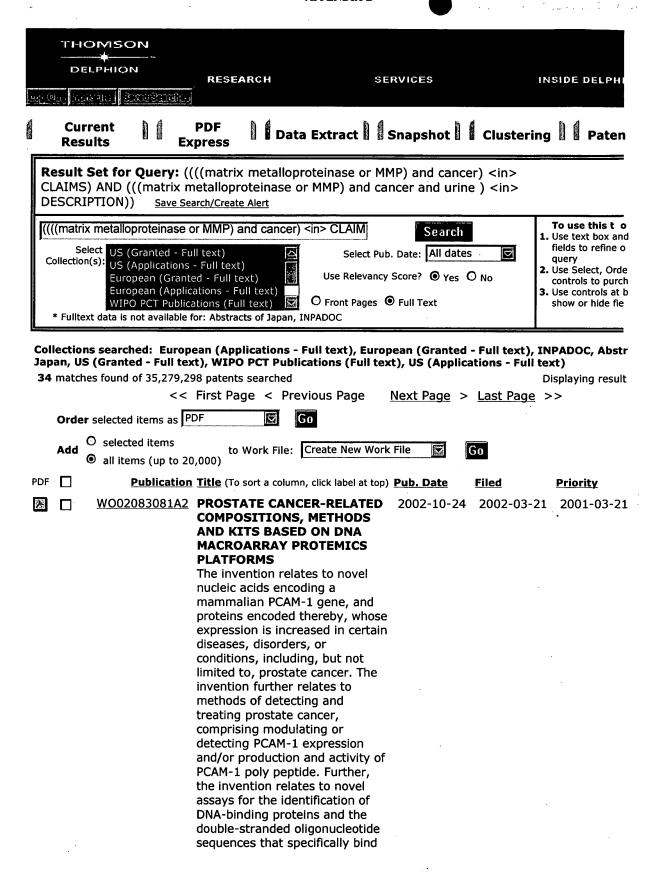
APPENDIX B



with them. [Show in French] **WO0231507A2 NON-INVASIVE ENZYME** 图 🗆 2002-04-18 2001-10-15 2000-10-13 **SCREEN FOR TISSUE REMODELLING-ASSOCIATED** CONDITIONS methods and kits for diagnosing the presence of and prognosing the appearance of tissue remodelling-associated conditions, involving the presence of enzyme complexes in a biological sample, are disclosed. In particular, the method pertains to diagnosing the presence of or prognosing appearance of metastatic cancer by the identification of high molecular weight enzyme complexes comprising MMPs. [Show in French] WO0168145A2 PEPTIDASE-CLEAVABLE, 2001-09-20 2001-03-15 2000-03-15 TARGETED ANTINEOPLASTIC **DRUGS AND THEIR** THERAPEUTIC USE This invention is directed to antineoplastic agents conjugated to enzyme-cleavable peptides comprising the amino acid recognition sequence of a membrane-bound and/or cellsecreted peptidase, and to the use of such conjugated compounds as chemotherapeutic agents in the targeted treatment of cancers. [Show in French] WO0023613A1 A METHOD OF ASSESSING A 2000-04-27 1999-10-19 1998-10-19 MATTER ASSOCIATED WITH **PARTURITION IN A** PREGNANT INDIVIDUAL The invention relates to a method of assessing a matter associated with parturition in a pregnant individual. The method involves the steps of measuring the level of at least one matrix proteinase in a body fluid sample from the individual to obtain test data and utilising the test data to make the assessment. The body fluid used in the method will typically be urine obtained from the relevant individual. [Show in French] ☐ US20020081641A1 Non-invasive enzyme screen 2002-06-27 2001-10-15

for tissue remodellingassociated conditions

Methods and kits for diagnosing the presence of and prognosing the appearance of tissue remodelling-associated conditions, involving the presence of enzyme complexes in a biological sample, are disclosed. In particular, the method pertains to diagnosing the presence of or prognosing appearance of metastatic cancer by the identification of high molecular weight enzyme complexes comprising MMPs.

E

WO0154712A1 COMPOSITIONS AND METHODS FOR THE EARLY DIAGNOSIS OF OVARIAN CANCER

The disclosed nucleic acid primer sets, used in combination with quantitative amplification (PCR) of tissue cDNA, can indicate the presence of specific proteases in a tissue sample. The detected proteases are themselves specifically overexpressed in certain cancers, and their presence may serve for early detection of associated ovarian and other malignancies, and for the design of interactive therapies for cancer treatment. [Show in French]

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W09741441A1 NONINVASIVE ENZYME SCREEN FOR TISSUE REMODELLINGASSOCIATED **CONDITIONS**

Methods and kits for diagnosing the presence of and prognosing the appearance of tissue remodellingassociated conditions, involving the presence of enzymes in a biological sample, are disclosed. In particular, the method pertains to diagnosing the presence of or prognosing appearance of cancer, metastatic cancer, and obstructive and degenerative conditions. [Show in French]

WO0166657A2 ALKYLENIMINE/ORGANIC **BARRIER COATINGS HAVING BIS-SILANE ADDITIVES**

2001-08-02 2001-01-26 2000-01-27

1997-11-06 1997-04-25 1996-04-26

2001-09-13 2001-02-21 2000-03-03

A composition which provides gas, flavor, and aroma barrier to substrates, where the composition is formed by mixing an ethylenically unsaturated acid, a bis-silane and a polyamine. [Show in French]

8

WO0166557A1 ADAM POLYNUCLEOTIDES, **POLYPEPTIDES, AND ANTIBODIES**

2001-09-13 2001-02-22 2000-03-03

The present invention relates to novel human ADAM polypeptides and isolated nucleic acids containing the coding regions of the genes encoding such polypeptides. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human ADAM polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human ADAM polypeptides. [Show in French]

WO0037107A2 METHOD OF USING A **CYCLOOXYGENASE-2 INHIBITOR AND A MATRIX METALLOPROTEINASE INHIBITOR AS A COMBINATION THERAPY IN** THE TREATMENT OF **NEOPLASIA**

> The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of a cyclooxygenase-2 inhibitor, a matrix metalloproteinase inhibitor and an antineoplastic agent.

[Show in French]

A

USH1973 Human neutrophil collagenase splice variant

The subject invention is related to human MMP-8alt genes and gene products and their differential expression when comparing a patient with a disease state to a control. A further aspect of the invention concerns compounds which antagonize the biological activity of MMP-8alt protein and methods 2000-06-29 1999-12-22 1998-12-23

2001-07-03 1998-10-22

for identifying these compounds. Another aspect of the present invention concerns pharmaceutical compositions comprising such compounds for the treatment of arthritis, cancer, and disease caused by cellular apoptosis including but not limited to Parkinson's disease, Alzheimer's disease and Huntington's chorea.

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WO0038719A1 USE OF A MATRIX **METALLOPROTEINASE INHIBITOR AND AN INTEGRIN ANTAGONIST IN** THE TREATMENT OF **NEOPLASIA**

> The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of a matrix metalloproteinase inhibitor, an integrin antagonist and an antineoplastic agent. [Show in French]

WO0020860A1 DIAGNOSTIC ASSAY FOR MATRIX METALLOPROTEINASE 9 AND USE THEREOF

The present invention employs an improved immunoassay that detects all forms of MMP-9 (both the form complexed with TIMP and the "free" uncomplexed form) in biological samples including human serum and plasma. Using this immunoassay the present inventors have surprisingly discovered that a much higher degree of detection and quantification is possible than with prior assays. The assay is preferably a capture assay using two antibodies to MMP-9 that do not compete with each other (i.e., bind to distinct epitopes). The epitopes that are bound to must be exposed in both the complexed MMP-9 as well as the free MMP-9.

[Show in French]

WO0182911A2 TREATMENT OF PATHOLOGICAL CONDITIONS INFLUENCED BY THE ACTION OF MATRIX METALLOPROTEINASES

2000-07-06 1999-12-22 1998-12-23

2000-04-13 1999-10-07 1998-10-08

2001-11-08 2001-04-30 2000-04-28

(MMPs) USING CLIOQUINOL

A use of clioquinol for the manufacture of a pharmaceutical composition for the prevention or the treatment of pathological conditions influenced by the action of matrix metalloproteinases (MMPs) is disclosed. Also methods of treatment or prevention of such conditions are disclosed. [Show in French]

28

WO0182912A2 TREATMENT OF **PATHOLOGICAL CONDITIONS INFLUENCED BY THE ACTION OF MATRIX METALLOPROTEINASES**

(MMPs) USING **PHANQUINONE**

A use of phanquinone for the manufacture of a pharmaceutical composition for the prevention or the treatment of pathological conditions influenced by the action of matrix metalloproteinases (MMPs) is disclosed. Also methods of treatment or prevention of such conditions are disclosed. [Show in French]

WO0149284A1 COMPOSITION FOR STABILIZING AND POTENTIATING THE ACTION **OF ANTI-ANGIOGENIC** SUBSTANCES BY **POLYUNSATURATED FATTY ACIDS**

> A method of stabilizing and potentiating action of molecules of known anti-angiogenic substances such as Angiostatin® or Endostatin® by using in coupling conjugation with cisunsaturated fatty acids (c-UFAs) in the treatment of cell proliferative disorders uses c-UFAs chosen from linoleic acid, gamma-linolenic acid, dihomogamma-linolenic acid, arachidonic acid, alpha-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid and cisparinaric acid in predetermined quantities. Preferably, the c-UFAs are in the form of polyunsaturated fatty acids (PUFAs). Uncontrolled or

2001-11-08 2001-04-30 2000-04-28

2001-07-12 2000-01-18 2000-01-05

undesirable angiogenic activity promotes cell proliferative disorders and tumor growth, which can be inhibited by the selective use of PUFAs with antiangiogenic substances used selectively in conjunction with predetermined anti-cancer drugs. For treatment of glioma, a sodium salt of a PUFA is preferred to form an admixture with an anti-angiogenic substance and a selected anticancer drug. For a non-glioma type of cell proliferation disorder, a sodium, potassium or lithium salt of a PUFA is preferred to form an admixture with an antiangiogenic substance. Antiangiogenic substances envisaged in this invention include Angiostatin®, Endostatin®, platelet factor-4, TNP-470, thalidomide, interleukin-12 and metalloproteinase inhibitors (MMP). A preferred method of administration of the mixture to treat a tumor is intra-arterial administration into an artery which provides the main blood supply for the tumor. [Show in French]

&

WO0038718A2 METHOD OF USING A MATRIX 2000-07-06 1999-12-22 1998-12-23 **METALLOPROTEINASE INHIBITOR AND ONE OR** MORE ANTINEOPLASTIC **AGENTS AS A COMBINATION** THERAPY IN THE TREATMENT OF NEOPLASIA

> The present invention provides methods to treat or prevent neoplasia disorders in a mammal using a combination of a matrix metalloproteinase inhibitor and an antineoplastic agent.

[Show in French]

WO02085386A2 sETHOD OF INDUCTION OF **APOPTOSIS AND INHIBITION** OF MATRIX **METALLOPROTEINASES USING ANTIMICROBIAL METALS**

> The invention relates to a method to induce apoptosis and to inhibit matrix metalloproteinases in a disease

2002-10-31 2002-04-23 2001-04-23

condition in a human or animal by contacting hyperplastic tissue, tumor tissue, or a cancerous lesion with one or more antimicrobial metals, preferably formed with atomic disorder, and preferably in a nanocrystalline form. The nanocrystalline antimicrobial metal of choise may be used in the form of a nanocrystalline coating of one or more antimicrobial metals, a nanocrystalline powder of one or more antimicrobial metals, or a solution containing dissolved species from a nanocrystalline powder or coating of one or more antimicrobial metals. [Show in French]

 □ US20020114848A1 Methods for regulating levels 2002-08-22 2001-11-21 of zinc, cadmium and calcium in humans and for diagnosing, or screening for the risk of developing, diseases associated with abnormal levels of cadmium, zinc and calcium in body fluids and tissues

> Methods and compositions are provided for decreasing PGE2:PGF2a, regulating ratios of zinc:cadmium and regulating the concentration of zinc, calcium and zinc-containing and PGE2dependent matrix metalloproteinases in body fluids and tissues of a human. Elevated or otherwise unregulated levels of PGE2, zinc and calcium and elevated concentrations of zinc-

diseases.

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p75 NEUROTROPHIN **RECEPTOR**

containing and PGE2-dependent matrix metalloproteinases have been found to be associated with the development of certain

The present invention provides an isolated protein comprising a pro-domain of a proneurotrophin, methods for producing the protein, and pharmaceutical compositions containing the isolated protein.

WO02096356A2 HIGH AFFINITY LIGAND FOR 2002-12-05 2002-05-24 2001-05-25

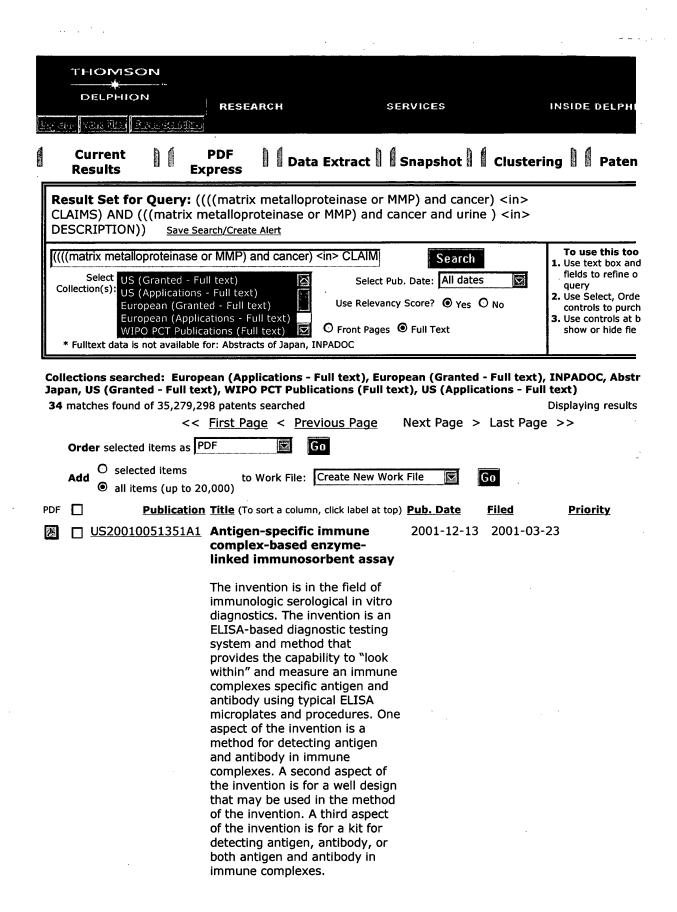
The invention also provides a nucleic acid molecule which encodes the protein and a vector containing the nucleic acid molecule. The present invention further provides a method for cleaving a proneurotrophin protein to a mature neurotrophin. In addition, the invention relates to methods for inducing apoptosis in a cell of a mammal expressing p75 surface receptors or p75 and trk receptors. The methods include causing the p75 receptor to bind a pharmaceutical composition containing a pro-domain of a proneurotrophin or administering to the mammal an effective amount of a cleavage-resistant proneurotrophin and an inhibitor of trk activation. The invention also relates to a method for inhibiting apoptosis of a cell in a mammal by administering an effective amount of a molecule which inhibits binding of a proneurotrophin to a p75 receptor. Also provided, are kits and methods for screening a human for a condition associated with undesired apoptosis. [Show in French]

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WOO173437A2 ANTIGEN-SPECIFIC IMMUNE A COMPLEX-BASED ENZYME-LINKED IMMUNOSORBENT **ASSAY**

The invention is in the field of immunologic serological in vitro diagnostics. The invention is an ELISA-based diagnostic testing system and method that provides the capability to "look within" and measure an immune complexes specific antigen and antibody using typical ELISA microplates and procedures. One aspect of the invention is a method for detecting antigen and antibody in immune complexes. A second aspect of the invention is for a well design that may be used in the method of the invention. A third aspect of the invention is for a kit for detecting antigen, antibody, or both antigen and antibody in immune complexes. [Show in French]

2001-01-18 2000-07-07 1999-07-09

2001-10-04 2001-03-23 2000-03-27

WO0103708A1 CADMIUM CONTAINING COMPOSITIONS

Methods and compositions are provided for decreasing or regulating ratios of zinc:cadmium and PGE2:PGF2a and regulating the concentration of zinc-containing and PGE2dependent matrix metalloproteinases in body fluids and tissues of a mammal, comprising administering to the mammal an amount of a pharmaceutically acceptable and bioavailable cadmium salt. Elevated or fluctuating levels of PGE2 and zinc and elevated concentrations of zinc-containing and PGE2-dependent matrix metalloproteinases have been found to be associated with the development of certain diseases. [Show in French]

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WO0010506A2 ANGIOGENESIS INHIBITORS AND USES THEREOF

The present invention features isolated angiogenesis inhibitors having a molecular weight of between about 40 kDa to 50 kDa and having an amino acid sequence substantially similar to

2000-03-02 1999-08-19 1998-08-20

that of the amino acid sequence shown in SEQ ID NO.2 or SED ID NO.3. Further provided are methods of making and using the angiogenesis inhibitors, e.g., to inhibit vascularization or to block osteonectin and plasminogen interaction. [Show in French]

WO02053152A1 COMPOSITION CONTAINING **FLAVONOIDS FOR** TREATMENT BRAIN **DISORDERS**

2002-07-11 2001-01-08

The present invention relates to a pharmaceutical composition for use (or when in use) in the treatment of brain disorders, said composition comprising one or more flavonoids admixed with a pharmaceutically acceptable diluent, excipient or carrier. The invention also relates to a process for the preparation of said pharmaceutical composition. A further aspect of the invention relates to the use of one or more flavonoids in the preparation of a medicament for treating brain disorders, and to a method of treating a brain disorder, said method comprising administering to a subject in need of treatment a therapeutically effective amount of one or more flavonoids. [Show in French]

WO0142438A2 LEUKOLYSIN/MMP25/MT6-**MMP**

2001-06-14 2000-12-13 1999-12-13

A novel compound, leukolysin, and therapeutic methods for treating conditions associated with the presence or absence of leukolysin is provided. Also provided are methods to detect or monitor inflammatory disease by determining the presence or amount of leukolysin in a physiological sample. [Show in French]

2

WO0232953A2 PREGNANCY-ASSOCIATED PLASMA PROTEIN-A2 (PAPP-**A2)**

The present invention provides nucleotide and amino acid sequences that identify and encode a new protein with homology to pregnancy2002-04-25 2001-10-19 2000-10-20

associated plasma protein-A (PAPP-A). We denote this protein PAPP-A2. The cDNA encoding PAPP-A2 was derived from human placenta. The present invention also provides for antisense molecules to the nucleotide sequences which encode PAPP-A2, expression vectors for the production of purified PAPP-A2, antibodies capable of binding specifically to PAPP-A2, hybridization probes or oligonucleotides for the detection of PAPP-A2-encoding nucleotide sequences, genetically engineered host cells for the expression of PAPP-A2, use of the protein to produce antibodies capable of binding specifically to the protein, methods for screening for pathologies in pregnant and non-pregnant patients that are based on detection of PAPP-A2 antigen in human body fluids or PAPP-A2encoding nucleic acid molecules, use of the protein to screen for agents that alter the protease activity of PAPP-A2, use of the protein as a therapeutic target for such agents, and use of the protein as a therapeutic agent in relevant pathological states. Methods for screening for altered focal proliferation states in pregnant and/or non-pregnant patients, which include detecting levels of PAPP-A2, are also described. The present invention also provides the identification of a natural substrate of PAPP-A2, insulin-like growth factor binding protein (IGFBP)-5. [Show in French]

EP1172361A1 SULFONAMIDE DERIVATIVES HAVING OXADIAZOLE RINGS

Sulfonamide derivatives having a matrix metalloprotease inhibiting effect, which are compounds represented by general formula (I), optical isomers of the same, pharmaceutically acceptable salts of both, or solvates of them: wherein R1 and R2 are each independently hydrogen

2002-01-16 2000-04-13 1999-04-19

atom, optionally substituted lower alkyl or the like; R3 is optionally substituted aryl, optionally substituted heteroaryl or the like; X is -CH=CH-, -O-, or -S-; Y is NHOH, hydroxy, or lower alkyloxy

EP1085097A1 Method for judging effectiveness of protease inhibitors

A method for judging effectiveness of a drug having protease inhibitory activity, which comprises the steps of: (1) bringing a biosample isolated or collected from a patient with a disease in which participation of a protease is suspected into contact with a thin membrane containing a protease substrate and formed on a surface of a support; (2) detecting a trace of digestion formed on the thin membrane by action of a protease; and (3) judging that a drug having protease inhibitory activity is effective for the patient when a trace of digestion is formed on the thin membrane. The method enables accurate judgment as to whether or not a drug having protease inhibitory activity is effective for a patient with a disease in which participation of a protease is suspected such as rheumatoid arthritis and cancer before administration of the drug.

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WO9712861A1 MERCAPTOAMIDE **DERIVATIVES AND THEIR** THERAPEUTIC USE

Mercaptoamide derivatives of formula (I), in which Y represents CHOH, CHNH2 or C=O and the other variables are defined in the description, have therapeutic activity as metalloproteinase, TNFalpha and Lselectin sheddase inhibitors. [Show in French]

WO9635714A1 PEPTIDE COMPOUNDS WHICH INHIBIT **METALLOPROTEINASE AND** TNF LIBERATION AND THEIR THERAPEUTIC USES

Tripeptidyl derivatives having a SH or acylS group and which

2001-03-21 2000-08-18 1999-08-18

1997-04-10 1996-10-04 1995-12-15

1996-11-14 1996-05-10 1995-05-10

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			inhibitors of matrix metalloproteinases and TNF. [Show in French]			
			THEIR THERAPEUTIC USE AS INHIBITORS OF METALLOPROTEASES Compounds of general formula (I) have utility as			
器		WO9611209A1	METALLOPROTEINASE AND TNF LIBERATION, AND THEIR THERAPEUTIC USE Peptidyl compounds have therapeutic utility via MMP/TNF inhibition. [Show in French] PEPTIDYL COMPOUNDS AND	1996-04-18	1995-10-05	1994-10-05
8		WO9635711A1	[Show in French] PEPTIDE COMPOUNDS WHICH INHIBIT	1996-11-14	1996-05-10	1995-05-10
* initial			WHICH INHIBIT METALLOPROTEINASE AND TNF LIBERATION AND THEIR THERAPEUTIC USE Dipeptidyl derivatives having a SH or acylS group and which are amides, thioamides or S(O) 0-2-amides, have therapeutic utility via MMP or TNF inhibition.			
28	П	WO9635712A1	are amides have therapeutic utility via MMP or TNF inhibition. [Show in French] PEPTIDYL COMPOUNDS	1996-11-14	1996-05-10	1995-05-10

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